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**6-SUBSTITUTED ACYCLICPYRIMIDINE NUCLEOSIDE DERIVATIVES AND ANTIVIRAL AGENTS
CONTAINING SAME AS ACTIVE INGREDIENTS.**

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JP-A- 6 156 171 JP-A-49 366 85</p> <p>(23) Proprietor: MITSUBISHI KASEI CORPORATION
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Description

TECHNICAL FIELD

- 5 The present invention relates to novel 6-substituted acyclopyrimidine derivatives, antiviral agents containing the derivatives as the active ingredients and a process for preparation of the derivatives.

BACKGROUND ART

- 10 Infectious diseases caused by human acquired immunodeficiency virus (HIV), which is a type of retrovirus, have recently become a serious social problem. A compound of 3'-deoxy-3'-azidothymidine is known as a nucleoside compound used in the clinical treatment of HIV-infection. However, this compound has side-effects since it also exhibits considerable toxicity in the host cell.

- 15 Although some 2',3'-dideoxyribonucleosides are known as nucleoside compounds exhibiting an anti-retroviral activity, it is still necessary to develop a substance possessing a higher activity and lower toxicity to the host cell (Hiroaki Mitsuya, *Bodily Defense*, Vol. 4, pp. 213 to 223 (1987)).

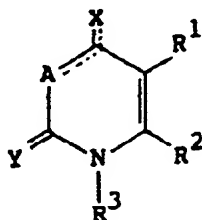
- On the other hand, various acyclonucleoside compounds have been synthesized since Acyclovir (acycloguanosine) was developed as an antiviral substance effective against herpes virus (C.K. Chu and S.J. Culter, *J. Heterocyclic Chem.*, 23, p. 289 (1986)). However, no acyclonucleoside compound having a
20 sufficient activity especially against retroviruses has yet been discovered.

EP-A 46307 (or US-A 4415573), EP-A 49072, (or US-A 4347360), and EP-A 167385 disclose acyclopyrimidine nucleoside derivatives with some antiviral activity.

- We have focussed our attention on 6-substituted acyclopyrimidine nucleoside compounds and have synthesized various novel 6-substituted acyclopyrimidine nucleoside derivatives and screened those compounds to detect an effective antiviral agent, especially to the retrovirus. Some 6-substituted acyclopyrimidine nucleoside compounds such as 6-fluoro substituted derivatives, 6-alkylamino substituted derivatives (DD-232492-A) and 6-methyl substituted derivatives (C.A. 107, 129717w (1987)), are known; however, the anti-retroviral activity of these compounds has not been described. As a result of our investigation, it was found that specific 6-substituted pyrimidine nucleoside compounds according to the
30 invention satisfy the above demand which enables one to provide effective anti-retroviral agents.

SUMMARY OF THE INVENTION

- 35 The present invention concerns a 6-substituted acyclopyrimidine nucleoside derivative represented by the following general formula I:



..... I

- 40 wherein R¹ represents a hydrogen or halogen atom or a group of alkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl; R² represents a group of arylthio, alkylthio, cycloalkylthio, aryl sulfoxide, alkyl sulfoxide, cycloalkyl sulfoxide, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or
45 aryloxy; R³ represents a hydroxyalkyl group of which alkyl portion may contain an oxygen atom; X represents an oxygen or sulfur atom or amino group; Y represents an oxygen or sulfur atom; and A represents =N- or -NH-, or a pharmaceutically acceptable salt thereof. Compounds according to claim 1, wherein:

- R¹ represents a hydrogen atom; halogen atom; C₁ to C₁₀ alkyl group; or a group of C₂ to C₅ alkenyl, C₂ to C₅ alkynyl, C₂ to C₅ alkylcarbonyl, C₇ to C₁₁ arylcarbonyl, C₈ to C₁₂ arylcarbonylalkyl, C₈ to C₁₀ arylthio or C₇ to C₁₂ aralkyl, those groups optionally substituted by one or more substituents selected from a halogen atom, C₁ to C₅ alkyl, C₁ to C₅ alkoxy, C₂ to C₆ alkoxycarbonyl, phenyl, naphthyl, carbamoyl, amino, nitro and cyano;

The group of R^1 represents a hydrogen atom; a halogen atom such as a chlorine, iodine, bromine and fluorine atom; an alkyl group such as a methyl, ethyl, n-propyl, i-propyl and n-butyl group; an alkenyl group such as vinyl, propenyl, butenyl, phenylvinyl, bromovinyl, cyanovinyl, alkoxy carbonylvinyl and carbamoylvinyl group; an alkynyl group such as an ethynyl, propynyl and phenylethynyl group; an alkylcarbonyl group such as an acetyl, propionyl and i-butyryl group; an arylcarbonyl group such as benzoyl and naphthoyl group; an arylcarbonylalkyl group such as a phenacyl group; an arylthio group such as a phenylthio, tolylthio and naphthylthio group; or an aralkyl group such as a benzyl group.

The group of R^2 represents an arylthio group such as a phenylthio and naphthylthio group, which may be optionally substituted with one or more substituents selected from a halogen atom such as a chlorine, iodine, bromine and fluorine atom, alkyl group such as a methyl, ethyl, propyl, butyl and pentyl group, halogenated alkyl group such as a trifluoromethyl group, alkoxy group such as a methoxy, ethoxy, propoxy and butoxy group, hydroxy group, nitro group, amino group, cyano group and acyl group such as an acetyl group; an alkylthio group such as a methylthio, ethylthio, propylthio, butylthio and pentylthio group; a cycloalkylthio group such as a cyclopentylthio, cyclohexylthio and cycloheptylthio group, which may be optionally substituted with one or more of the substituents mentioned above as the substituent of the arylthio group; an aryl sulfoxide group such as a phenyl sulfoxide group; an alkyl sulfoxide group such as a methyl sulfoxide, ethyl sulfoxide and butyl sulfoxide group; a cycloalkyl sulfoxide group such as cyclopentyl sulfoxide, cyclohexyl sulfoxide group; an alkenyl group such as vinyl, propenyl and phenylvinyl group; an alkynyl group such as an ethynyl, propynyl and phenylethynyl group; an aralkyl group such as a benzyl group; an arylcarbonyl group such as a benzoyl group; an arylcarbonylalkyl group such as a phenacyl group; or an aryloxy group such as a phenyloxy group.

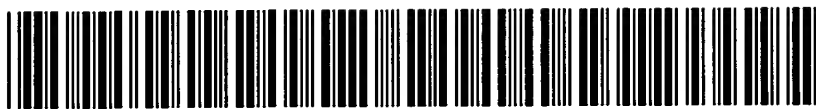
The group of R^3 represents a hydroxyalkyl group, preferably an ω -hydroxyalkoxy alkyl group such as (2-hydroxyethoxy)methyl, (3-hydroxypropoxy)methyl, (2,3-dihydroxypropoxy)methyl, 1-(2-hydroxyethoxy)ethyl, [2-hydroxy-1-(hydroxymethyl)ethoxy]methyl and (2-hydroxy-1-methylethoxy)methyl group.

The symbol of X represents an oxygen or sulfur atom or an amino group.

The symbol of Y represents an oxygen or sulfur atom.

The symbol of A represents =N- or -NH-.

The preferred compounds according to the invention have R^1 of a hydrogen atom, halogen atom, C_1 to C_5 alkyl group or C_2 to C_5 alkenyl group, particularly, C_1 to C_5 alkyl group; R^2 of C_6 to C_{10} arylthio, C_3 to C_{10} cycloalkylthio or C_7 to C_{11} aralkyl group, particularly those substituted with one or more substituents selected from halogen atom, C_1 to C_5 alkyl group, C_1 to C_5 alkoxy group and nitro group; R^3 of hydroxyalkoxyalkyl group having 2 to 6 carbon atoms, particularly 2-hydroxyethoxymethyl group; X of oxygen or sulfur atom; and Y of oxygen or sulfur atom.



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